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Synthesis of optically active trifluoromethyl-substituted 2,3-dihydroimidazo[2,1-*b*]oxazoles

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Abstract

The 2-unsubstituted imidazole *N*-oxides with a 3,3,3-trifluoro-2-hydroxypropyl group at N(1) in the presence of acetic anhydride undergo cyclization via the intramolecular nucleophilic attack of the hydroxyl group onto C(2) of the imidazole ring to give trifluoromethylated derivatives of 2,3-dihydroimidazo[2,1-*b*]oxazoles. This method, starting with enantiopure substrates, allows the preparation of enantiopure products in a one-pot procedure.

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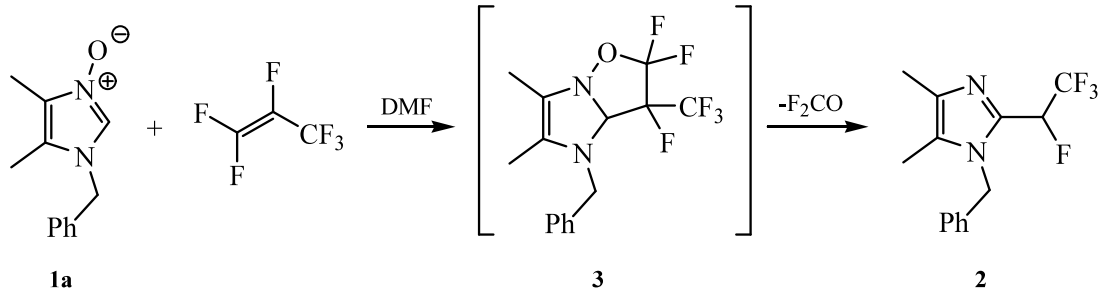
1. Introduction

The 2-unsubstituted imidazole *N*-oxides of type **1** (imidazole 3-oxides), constitute a class of imidazole derivatives, which can be considered as useful starting materials for the preparation of more complex imidazole derivatives [1]. They are conveniently accessible by condensation of N-substituted formaldimines with the corresponding α-hydroxy iminoketones. In terms of the reactivity, *N*-oxides **1** resemble aldonitrones, and therefore react with diverse dipolarophiles via a [3+2]-cycloaddition as the initial step of the conversion. For example, fluoroalkylated imidazole **2** can be obtained from **1a** and perfluoropropene after elimination of fluorophosgene from the initially formed [3+2]-cycloadduct **3** (Scheme 1) [2].



Scheme 1. Fluoroalkylation of an imidazole *N*-oxide via [3+2]-cycloaddition [2].

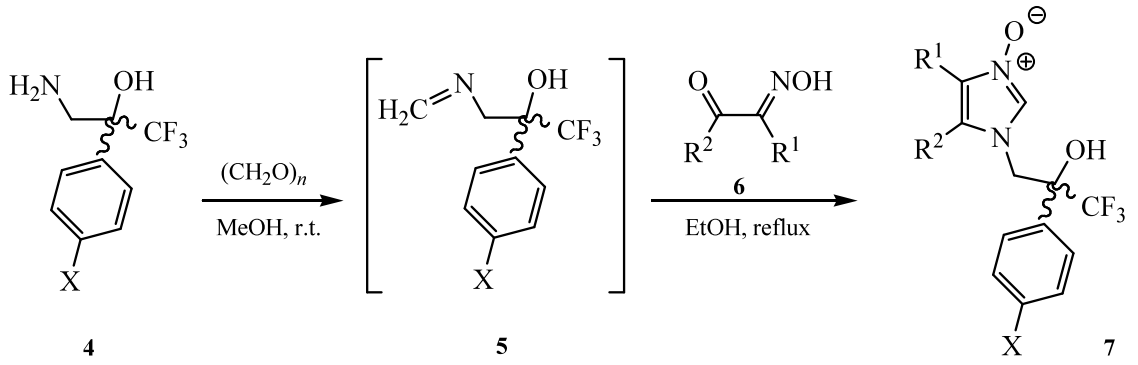
Another important conversion of *N*-oxides **1** is the rearrangement into isomeric imidazole-2-ones by treatment with acetic anhydride [3]. However, in the case of **1** bearing a β-hydroxyalkyl residue at N(1), the reaction with acetic anhydride leads to the intramolecular ring closure, and imidazo[2,1-*b*]oxazole derivatives are formed as final products [4]. In a recent publication, we reported on a similar ring closure via a nucleophilic attack of an amino group [5].

The aim of the present study was the synthesis of 2-trifluoromethyl-substituted imidazo[2,1-*b*]oxazoles via the acetic anhydride-initiated cyclization of selected 1-(3,3,3-trifluoro-2-hydroxypropyl)imidazole 3-oxides, especially of enantiopure substrates.

2. Results and discussion

In a recent publication, the synthesis of optically active imidazole *N*-oxides bearing a fluorinated hydroxyalkyl group at N(1) was described [6]. The preparation of the new series

of compounds **7** (Table 1) is presented in Scheme 2. In the first step, racemic or enantiopure β-amino alcohols **4** were treated with paraformaldehyde to give the corresponding formaldimines **5**. Subsequently, the latter were treated with α-hydroxy iminoketones **6** in boiling ethanol affording the desired products **7**. Starting with enantiopure substrates **4**, optically pure imidazole *N*-oxides **7** were obtained. Their enantiopurity was confirmed by ^{1}H NMR spectroscopy using a chiral agent [7].



Scheme 2. Synthesis of 1-(3,3,3-trifluoro-2-hydroxypropyl)imidazole 3-oxides **6**.

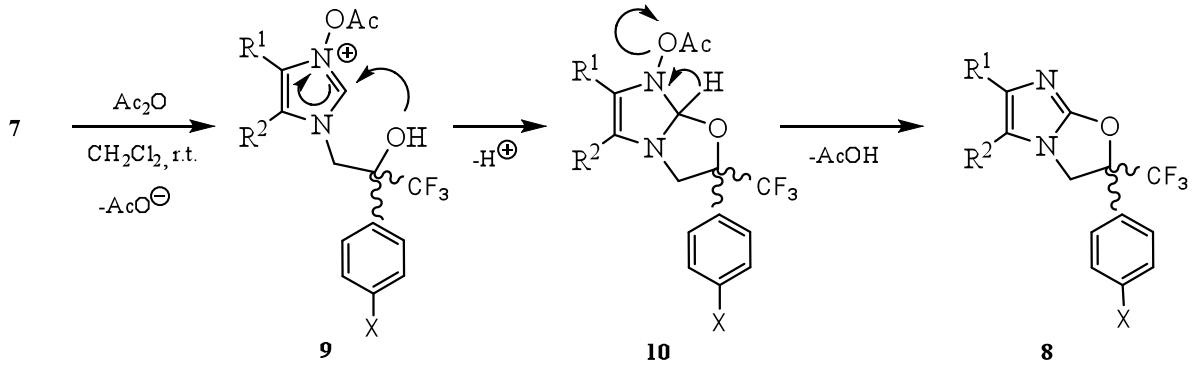
In a typical experiment, the racemic imidazole *N*-oxide **7a** in CH_2Cl_2 solution was treated with acetic anhydride in access at room temperature. The progress of the reaction was monitored by TLC, and after completion of the reaction, the crude product was analyzed by ^{1}H NMR and IR spectroscopy.

The IR spectrum of the obtained compound did not show the expected absorption band for the imidazolone isomeric with **7a**. Moreover, there were no absorption bands neither for hydroxyl nor ester groups detected. In the ^{1}H NMR spectrum in $CDCl_3$, the most characteristic feature was the presence of an AB system located at 4.83 and 4.50 ppm. Furthermore, the mass spectrum evidenced the formation of a product via elimination of water (*m/z* 407).

Table 1. Synthesis of imidazole 3-oxides **7** and their transformation into 2,3-dihydroimidazo[2,1-*b*]oxazoles **8**.

7	R^1	R^2	X	Yield [%]	**8**	Yield [%]
(*RS*)-**7a**	Ph	Ph	H	63	(*RS*)-**8a**	82
(*S*)-**7a**				60	(*S*)-**8a**	79
(*R*)-**7a**				59	(*R*)-**8a**	83
(*RS*)-**7b**	Ph	Ph	MeO	66	(*RS*)-**8b**	80
(*S*)-**7b**				67	(*S*)-**8b**	85
(*R*)-**7b**				69	(*R*)-**8b**	86
(*S*)-**7c**	Me	Me	MeO	71	(*S*)-**8c**	50
(*R*)-**7c**				75	(*R*)-**8c**	49
(*S*)-**7d**	Me	Ph	MeO	65	(*S*)-**8d**	79
(*R*)-**7d**				68	(*R*)-**8d**	80
(*S*)-**7e**	CONHPh	Me	H	59	(*S*)-**8e**	81
(*R*)-**7e**				61	(*R*)-**8e**	83

Based on these data, the structure of the imidazo[2,1-*b*]oxazole **8a** was proposed (Scheme 3). The ^{13}C NMR spectrum of the purified sample fitted well with this proposal. For example, the characteristic signals for sp^3-C-atoms C(2) and C(3) appeared at 92.1 and 51.2 ppm, respectively.



Scheme 3. Reaction mechanism for the formation of 2,3-dihydroimidazo[2,1-*b*]oxazoles **8**.

The same protocol was applied for the transformation of a series of enantiopure imidazole *N*-oxides **7**, and in all cases were optically active products obtained in good yields (Table 1).

The mechanistic explanation of the reaction pathway is presented in Scheme 3. The initial step of the multistep conversion is the formation of the reactive imidazolium cation **9**, with undergoes a cyclization via the nucleophilic attack of the OH-group onto the imidazolium C(2)-atom leading to the 1,3-oxazolidine ring of the bicyclic compound **10**. Apparently, this ring closure occurs faster than both the rearrangement to the imidazolone derivative [3] and the competitive acylation of the hydroxyl group [8]. Finally, elimination of AcOH leads to the bicyclic product **10**. All steps of the presented reaction occur with preservation of the configuration of the stereogenic centre.

3. Conclusion

The results of the present study show that the 2-unsubstituted imidazole *N*-oxides **7** bearing a fluorinated 2-hydroxalkyl group at N(1) can be efficiently transformed into hitherto unknown, trifluoromethyl-substituted imidazo[2,1-*b*]oxazole derivatives **8**. The starting materials **7** can be easily prepared in enantiopure form and, therefore, optically active products of type **8** are also accessible. It is well established that fluoroalkyl-substituted heterocycles found diverse applications, and for that imidazo[2,1-*b*]oxazole reason, products **8** are of potential interest in organic synthesis, medicinal chemistry and related fields [9]. The novel approach to this fused heterocyclic scaffold via properly substituted imidazole *N*-oxides supplements the earlier reported methods for their preparation based, e.g. on heterocylization of an imidazolone equivalent [10], reaction of dinitroimidazole with substituted oxiranes [11] or copper(I) catalyzed intramolecular alkoxylation of imidazoles [12].

Differently substituted imidazo[2,1-*b*]oxazoles display not only antibacterial and antitubercular activity [13] but they are also known as radiosensitizing agents [14]. In a very recent publication a series of trisubstituted imidazo[2,1-*b*]oxazoles, including fluorinated derivatives, has been described and the results of the study on their biological activities (new drug candidates for visceral leishmaniasis) were presented and discussed [15].

Acknowledgments

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4. Experimental part

4.1. General experimental procedures

Melting points were determined in a capillary using a Mel-Temp II (Aldrich) or STUART SMP30 apparatus and are uncorrected. The IR Spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions (ν) in cm^{-1}. The ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectra were measured on a Bruker Avance III instrument (600, 150, and 565 MHz, resp.) in CD_3OD, DMSO-d_6 or $CDCl_3$ using solvent signals as reference. The multiplicity of signals in the ^{13}C NMR spectra was established using the HMQC technique. Chemical shifts (δ) are given in ppm and coupling constants J in Hz. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. HR-ESI-MS: Bruker maxis spectrometer; ESI-MS: Varian 500. Optical rotations were determined on a PERKIN–ELMER 241 MC polarimeter for λ = 589 nm. All chromatographic separations were carried out on a column packed with silica gel.

4.2. General procedure for the synthesis of imidazole N-oxides **7**

To the solution of β-amino-α-trifluoromethyl alcohol **4** (1.0 mmol) in MeOH (3 ml) paraformaldehyde (1.0 mmol) was added at room temperature and the mixture was stirred overnight. Then, the solvent was evaporated and the obtained imine was dissolved in EtOH (4 ml). To this solution, an equimolar amount of the corresponding α-hydroxyimino ketone was added and the mixture was reflux for 3 h. Next, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (AcOEt/MeOH, 8:2).

*3-(4,5-Diphenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-phenylpropan-2-ol* ((*R,S*)-**7a**). Yield: 0.267 g (63%). Colorless crystals. Mp. 198–200 °C. IR (KBr): ν 3700–2000vs,br. with intense bands at 3420br, 3181m, 3061m; 1505m, 1489m, 1447s, 1404m, 1352s, 1270s,

1159s.br, 1052m, 864m, 760s, 699s, 652s, 513m. ^{1}H NMR (CD_3OD): δ 8.28 (s, 1H, HC(2)); 7.42–7.38 (m, 1H, HC(arom)); 7.34–7.29 (m, 3H, HC(arom)); 7.27–7.18 (m, 9H, HC(arom)); 6.93–6.89 (m, 2H, HC(arom)); 4.56 (br s, 2H, H_2C). ^{13}C NMR (CD_3OD): δ 134.4, 130.9, 129.8, 129.4, 129.3, 129.0, 128.9, 128.8, 128.6, 128.4, 128.1, 127.7, 126.2, 126.0, 125.9 (15 CH(arom), 3 C(arom), CH(imid), 2 C(imid)); 124.9 (q, $^{1}J_{C,F}$ = 284.9, CF_3); 76.4 (q, $^{2}J_{C,F}$ = 28.5, *C*CF_3); 49.6 (CH_2). ^{19}F NMR (CD_3OD): δ –78.2. HR-ESI-MS: 425.14712 (calcd 425.14714 for $C_{24}H_{20}O_2N_2F_3$, $[M+H]^+$).

*(*S*)-3-(4,5-Diphenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-phenylpropan-2-ol* ((*S*)-**7a**). Yield: 0.254 g (60%). Colorless crystals. Mp. 150–152 °C. IR (KBr): ν 3700–2000vs,br. with intense bands at 3421br, 3170m, 3060m; 1447m, 1402w, 1351m, 1267s, 1162s.br, 1053w, 864w, 761s, 699s, 651m, 513w. ^{1}H NMR (CD_3OD): δ 8.35 (s, 1H, HC(2)); 7.47–7.43 (m, 1H, HC(arom)); 7.39–7.35 (m, 3H, HC(arom)); 7.31–7.24 (m, 9H, HC(arom)); 6.97–6.94 (m, 2H, HC(arom)); 4.61 (br s, 2H, H_2C). ^{13}C NMR (CD_3OD): δ 134.4, 130.9, 129.8, 129.4, 129.3, 128.9, 128.8, 128.6, 128.4, 128.3, 128.1, 127.7, 126.2, 126.0, 125.9 (15 CH(arom), 3 C(arom), CH(imid), 2 C(imid)); 125.0 (q, $^{1}J_{C,F}$ = 285.0, CF_3); 76.4 (q, $^{2}J_{C,F}$ = 27.4, *C*CF_3); 49.6 (CH_2). ^{19}F NMR (CD_3OD): δ –78.1. HR-ESI-MS: 425.14704 (calcd 425.14714 for $C_{24}H_{20}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +60 (c 1.0, MeOH).

*(*R*)-3-(4,5-Diphenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-phenylpropan-2-ol* ((*R*)-**7a**). Yield: 0.250 g (59%). Colorless crystals. Mp. 138–140 °C. IR (KBr): ν 3700–2000vs,br. with intense bands at 3423br, 3170w, 3061w; 1447m, 1351m, 1267s, 1162s.br, 1053w, 864w, 761s, 700s, 651m, 513w. ^{1}H NMR ($CDCl_3$): δ 8.62 (s, 1H, HC(2)); 7.35–7.31 (m, 1H, HC(arom)); 7.24–7.20 (m, 2H, HC(arom)); 7.18–7.15 (m, 3H, HC(arom)); 7.09–6.97 (m, 7H, HC(arom)); 6.72–6.68 (m, 2H, HC(arom)); 4.43, 4.38 (AB, $J_{A,B}$ = 13.8, 2H, H_2C). ^{13}C NMR ($CDCl_3$): δ 134.4, 130.9, 129.8, 129.4, 129.3, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 127.7, 126.2, 126.0, 125.9 (15 CH(arom), 3 C(arom), CH(imid), 2 C(imid)); 124.9 (q, $^{1}J_{C,F}$ = 286.2, CF_3); 76.4 (q, $^{2}J_{C,F}$ = 28.0, *C*CF_3); 49.6 (CH_2). ^{19}F NMR ($CDCl_3$): δ –76.8. HR-ESI-MS: 425.14709 (calcd 425.14714 for $C_{24}H_{20}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –62 (c 1.0, MeOH).

*3-(4,5-Diphenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*RS*)-**7b**). Yield: 0.299 g (66%). Colorless crystals. Mp. 186–188 °C. IR (KBr): ν 3600–2700vs,br. with intense bands at 3420br, 3177w, 3058w, 2958w, 2839w; 1612s, 1515s,

1445s, 1351s, 1258s, 1159br. s, 1028m, 977w, 830m, 762s, 701s, 651s. ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H, HC(2)); 7.45–7.41 (m, 1H, HC(arom)); 7.37–7.33 (m, 2H, HC(arom)); 7.25–7.11 (m, 7H, HC(arom)); 6.94–6.89 (m, 2H, HC(arom)); 6.72–6.68 (m, 2H, HC(arom)); 4.56, 4.38 (AB, $J_{A,B}$ = 13.8, 2H, H_2C); 3.75 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 159.8, 131.0, 130.1, 129.5, 129.0, 128.9, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 126.8, 126.3, 113.8 (14 CH(arom), 4 C(arom), CH(imid), 2 C(imid)); 125.4 (q, $^{1}J_{C,F}$ = 286.3, CF_3); 76.2 (q, $^{2}J_{C,F}$ = 27.9, *C*CF_3); 54.9 (CH_3); 50.3 (CH_2). ^{19}F NMR ($CDCl_3$): δ –78.8. HR-ESI-MS: 455.15771 (calcd 455.15770 for $C_{25}H_{22}O_3N_2F_3$, $[M+H]^+$).

*(*S*)-3-(4,5-Diphenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*S*)-**7b**). Yield: 0.304 g (67%). Colorless crystals. Mp. 196–198 °C. IR (KBr): ν 3600–2500vs,br. with intense bands at 3423br, 3171w, 3058w, 2959w, 2839w; 1612m, 1515s, 1445m, 1351m, 1257s, 1173br. s, 1029w, 830w, 763m, 700m, 651m. ^{1}H NMR (CD_3OD): δ 8.26 (s, 1H, HC(2)); 7.41–7.37 (m, 1H, HC(arom)); 7.33–7.29 (m, 2H, HC(arom)); 7.26–7.18 (m, 5H, HC(arom)); 7.12–7.08 (m, 2H, HC(arom)); 6.95–6.91 (m, 2H, HC(arom)); 6.78–6.74 (m, 2H, HC(arom)); 4.53 (br s, 2H, H_2C); 3.73 (s, 3H, H_3C). ^{13}C NMR (CD_3OD): δ 160.3, 130.8, 129.8, 129.4, 129.0, 128.9, 128.6, 128.4, 128.2, 127.7, 127.2, 126.3, 126.1, 126.0, 113.7 (14 CH(arom), 4 C(arom), CH(imid), 2 C(imid)); 125.1 (q, $^{1}J_{C,F}$ = 284.9, CF_3); 76.2 (q, $^{2}J_{C,F}$ = 27.7, *C*CF_3); 54.5 (CH_2); 49.7 (CH_3). ^{19}F NMR (CD_3OD): δ –77.3. HR-ESI-MS: 455.15752 (calcd 455.15770 for $C_{25}H_{22}O_3N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +53 (c 1.0, MeOH).

*(*R*)-3-(4,5-Diphenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*R*)-**7b**). Yield: 0.313 g (69%). Colorless crystals. Mp. 204–206 °C. IR (KBr): ν 3600–2200vs,br. with intense bands at 3424br, 3193m, 3060w, 2960w, 2839w; 1611m, 1516s, 1445m, 1350m, 1258s, 1173br. s, 1030m, 833m, 763s, 699s, 650m. ^{1}H NMR (CD_3OD): δ 8.25 (s, 1H, HC(2)); 7.39–7.34 (m, 1H, HC(arom)); 7.31–7.27 (m, 2H, HC(arom)); 7.24–7.16 (m, 5H, HC(arom)); 7.11–7.07 (m, 2H, HC(arom)); 6.93–6.89 (m, 2H, HC(arom)); 6.76–6.72 (m, 2H, HC(arom)); 4.50 (br s, 2H, H_2C); 3.71 (s, 3H, H_3C). ^{13}C NMR (CD_3OD): δ 160.3, 130.8, 129.8, 129.4, 128.9, 128.8, 128.6, 128.4, 128.2, 127.7, 127.2, 126.3, 126.1, 126.0, 113.7 (14 CH(arom), 4 C(arom), CH(imid), 2 C(imid)); 125.1 (q, $^{1}J_{C,F}$ = 285.2, CF_3); 76.2 (q, $^{2}J_{C,F}$ = 27.7 *C*CF_3); 54.5 (CH_2); 49.7 (CH_3). ^{19}F NMR (CD_3OD): δ –78.4.

HR-ESI-MS: 455.15759 (calcd 455.15770 for $C_{25}H_{22}O_3N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –50 (c 1.0, MeOH).

*(*S*)-3-(4,5-Dimethyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*S*)-**7c**). Yield: 0.219 g (73 %). Colorless crystals, Mp. 232–235 °C (lit. [6], Mp. 234–236 °C(decomp.)).

*(*R*)-3-(4,5-Dimethyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*R*)-**7c**). Yield: 0.247 g (75%). Colorless crystals. Mp. 222–224 °C. IR (KBr): ν 3600–2000vs,br. with intense bands at 3451br, 3186m, 2960w, 2934w, 2837w; 1612m, 1514s, 1457m, 1386m, 1262br. s, 1154br. s, 1086s, 967m, 830s, 753m, 659s. ^{1}H NMR (CD_3OD): δ 7.68 (s, 1H, HC(2)); 7.41–7.37 (m, 2H, HC(arom)); 6.91–6.87 (m, 2H, HC(arom)); 4.44 (br s, 2H, H_2C); 3.75 (s, 3H, H_3C); 1.99 (s, 3H, H_3C); 1.92 (s, 3H, H_3C). ^{13}C NMR (CD_3OD): δ 160.4, 127.5, 126.6, 126.5, 124.8, 123.7, 113.6 (4 CH(arom), 2 C(arom), CH(imid), 2 C(imid)); 125.3 (q, $^1J_{C,F}$ = 284.9, CF_3); 76.5 (q, $^2J_{C,F}$ = 27.6, CCF_3); 54.4 (CH_2); 49.6 (CH_3); 7.2 (CH_3); 5.6 (CH_3). ^{19}F NMR (CD_3OD): δ –78.2. HR-ESI-MS: 331.12620 (calcd 331.12640 for $C_{15}H_{18}O_3N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –21 (c 1.0, MeOH).

*(*S*)-3-(5-Methyl-4-phenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*S*)-**7d**). Yield: 0.255 g (65%). Colorless crystals. Mp. 88–90 °C. IR (KBr): ν 3600–2000vs,br. with intense bands at 3416br, 3060m, 2976m, 2865w; 1624w, 1498m, 1448m, 1402m, 1352s, 1267br. s, 1154br. s, 1028m, 971w, 765s, 698s, 656m. ^{1}H NMR (CD_3OD): δ 8.11 (s, 1H, HC(2)); 7.48–7.41 (m, 3H, HC(arom)); 7.06–7.02 (m, 4H, HC(arom)); 6.75–6.71 (m, 2H, HC(arom)); 4.52, 4.46 (AB, J_{AB} = 14.4, 2H, H_2C); 3.76 (s, 3H, H_3C); 1.97 (s, 3H, H_3C). ^{13}C NMR (CD_3OD): δ 160.2, 130.2, 129.3, 128.7, 128.1, 127.4, 127.2, 126.4, 126.3, 125.9, 113.6 (9 CH(arom), 3 C(arom), CH(imid), 2 C(imid)); 125.0 (q, $^1J_{C,F}$ = 285.2, CF_3); 76.1 (q, $^2J_{C,F}$ = 27.8, CCF_3); 54.4 (CH_3); 49.6 (CH_2); 6.1 (CH_3). ^{19}F NMR (CD_3OD): δ –78.7. HR-ESI-MS: 393.14186 (calcd 393.14205 for $C_{20}H_{20}O_3N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +70 (c 1.0, MeOH).

*(*R*)-3-(5-Methyl-4-phenyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*R*)-**7d**). Yield: 0.266 g (68%). Pale yellow oil. IR (film): ν 3600–2200vs,br. with intense bands at 3423br, 3060w, 2865w; 1623w, 1498w, 1448w,

1401w, 1351m, 1267br. s, 1154br. s, 1028w, 971w, 765s, 698s, 656m. ^{1}H NMR (CD_3OD): δ 8.04 (s, 1H, HC(2)); 7.39–7.34 (m, 3H, HC(arom)); 6.99–6.95 (m, 4H, HC(arom)); 6.68–6.64 (m, 2H, HC(arom)); 4.45, 4.39 (AB, J_{AB} = 14.6, 2H, H_2C); 3.69 (s, 3H, H_3C); 1.90 (s, 3H, H_3C). ^{13}C NMR (CD_3OD): δ 160.2, 130.2, 129.2, 128.7, 128.0, 127.4, 127.2, 126.4, 126.3, 125.9, 113.6 (9 CH(arom), 3 C(arom), CH(imid), 2 C(imid)); 125.1 (q, $^{1}J_{C,F}$ = 285.3, CF_3); 76.1 (q, $^{2}J_{C,F}$ = 27.5, CCF_3); 54.4 (CH_3); 49.6 (CH_2); 6.1 (CH_3). ^{19}F NMR (CD_3OD): δ –77.1. HR-ESI-MS: 393.14213 (calcd 393.14205 for $C_{20}H_{20}O_3N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –69 (c 1.0, MeOH).

*(*S*)-5-Methyl-3-oxy-1-(3,3,3-trifluoro-2-hydroxy-2-phenylpropyl)-1*H*-imidazole-4-carboxylic acid phenylamide* ((*S*)-**7e**). Yield: 0.239 g (59%). Colorless crystals. Mp. 264–266 °C. IR (KBr): ν 3600–2500vs,br. with intense bands at 3247br, 3109m, 3044s, 2966m; 1681s, 1618s, 1592s, 1564s, 1448s, 1315s, 1269s, 1164s, 1024m, 977m, 760s, 702s, 630s. ^{1}H NMR (DMSO-d_6): δ 13.40 (s, 1H, NH); 8.07 (s, 1H, HC(2)); 7.62–7.55 (m, 4H, HC(arom)); 7.48–7.42 (m, 3H, HC(arom)); 7.35–7.30 (m, 2H, HC(arom)); 7.10–7.06 (m, 1H, HC(arom)); 4.69, 4.65 (AB, J_{AB} = 15.0, 2H, H_2C); 2.34 (s, 3H, H_3C). ^{13}C NMR (DMSO-d_6): δ 157.7 (C=O); 138.6, 135.3, 133.3, 129.8, 129.5, 129.0, 127.6, 126.9, 124.1, 120.1, 119.9 (10 CH(arom), 2 C(arom), CH(imid), 2 C(imid)); 125.6 (q, $^{1}J_{C,F}$ = 286.2, CF_3); 76.6 (q, $^{2}J_{C,F}$ = 26.9, CCF_3); 49.3 (CH_2); 9.8 (CH_3). ^{19}F NMR (DMSO-d_6): δ –76.3. HR-ESI-MS: 406.13666 (calcd 406.13730 for $C_{20}H_{19}O_3N_3F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +21 (c 1.0, MeOH).

*(*R*)-5-Methyl-3-oxy-1-(3,3,3-trifluoro-2-hydroxy-2-phenylpropyl)-1*H*-imidazole-4-carboxylic acid phenylamide* ((*R*)-**7e**). Yield: 0.247 g (61%). Colorless crystals. Mp. 258–260 °C. IR (KBr): ν 3600–2600vs,br. with intense bands at 3248br, 3109m, 3044m, 2966m; 1681s, 1618s, 1592s, 1564s, 1501m, 1448m, 1315s, 1269s, 1204s, 1157s, 1024m, 977m, 760s, 702s, 630s. ^{1}H NMR (DMSO-d_6): δ 13.40 (s, 1H, NH); 8.07 (s, 1H, HC(2)); 7.63–7.56 (m, 4H, HC(arom)); 7.48–7.45 (m, 3H, HC(arom)); 7.35–7.30 (m, 2H, HC(arom)); 7.10–7.06 (m, 1H, HC(arom)); 4.69, 4.66 (AB, J_{AB} = 15.0, 2H, H_2C); 2.35 (s, 3H, H_3C). ^{13}C NMR (DMSO-d_6): δ 157.1 (C=O); 138.0, 134.8, 132.8, 129.2, 129.0, 128.5, 127.0, 126.4, 123.6, 119.5, 119.4 (10 CH(arom), 2 C(arom), CH(imid), 2 C(imid)); 125.0 (q, $^{1}J_{C,F}$ = 285.6, CF_3); 76.0 (q, $^{2}J_{C,F}$ = 27.3, CCF_3); 48.8 (CH_2); 9.3 (CH_3). ^{19}F NMR (DMSO-d_6): δ –75.6. HR-ESI-MS: 406.13704 (calcd 406.13730 for $C_{20}H_{19}O_3N_3F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –23 (c 1.0, MeOH).

4.3. General procedure for the synthesis of trifluoromethylated 2,3-dihydroimidazo[1,3-oxazole] derivatives **8**.

To a solution of the corresponding imidazole *N*-oxide **7** (1 mmol) in CH_2Cl_2 (5 ml), freshly distilled acetic anhydride (10 ml) was added at room temperature. After all of **7** was consumed (monitored by TLC), MeOH (5 ml) was added to the mixture and stirring was continued for 30 min. Next, the solvent was evaporated and the crude product was purified by column chromatography (hexane/AcOEt, 7:3).

*2,5,6-Triphenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*R*,*S*)-**8a**). Yield: 0.332 g (82%). Colorless crystals. Mp. 152–154 °C. IR (KBr): ν 3060br.w, 1604s, 1587s, 1570m, 1499s, 1343s, 1303s, 1204vs, 1191vs, 1170s, 1062s, 1006s, 974m, 774m, 700s. ^{1}H NMR ($CDCl_3$): δ 7.65–7.58 (m, 4H, HC(arom)); 7.53–7.49 (m, 3H, HC(arom)); 7.44–7.35 (m, 5H, HC(arom)); 7.29–7.25 (m, 2H, HC(arom)); 7.24–7.20 (m, 1H, HC(arom)); 4.83, 4.50 (AB, J_{AB} = 10.2, 2H, H_2C). ^{13}C NMR ($CDCl_3$): δ 157.3, 138.5, 134.5, 133.6, 130.3, 130.2, 129.1, 129.0, 128.3, 128.2, 128.1, 127.2, 126.9, 126.0, 121.8 (15 CH(arom), 3 C(arom), 3 C(imid)); 123.4 (q, $^1J_{C,F}$ = 282.5, CF_3); 92.1 (q, $^2J_{C,F}$ = 31.1, *C*CF_3); 51.2 (CH_2). ^{19}F NMR ($CDCl_3$): δ –80.7. HR-ESI-MS: 407.13573 (calcd 407.13657 for $C_{24}H_{18}ON_2F_3$, $[M+H]^+$).

*(*S*)-2,5,6-Triphenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*S*)-**8a**). Yield: 0.321 g (79%). Colorless oil. IR (film): ν 3062br.w, 2903w, 1606s, 1590s, 1572s, 1500s, 1443m, 1340s, 1305s, 1197vs, 1177vs, 1063s, 1009s, 974m, 910m, 738s, 700s. ^{1}H NMR ($CDCl_3$): δ 7.64–7.62 (m, 2H, HC(arom)); 7.60–7.58 (m, 2H, HC(arom)); 7.53–7.49 (m, 3H, HC(arom)); 7.44–7.35 (m, 5H, HC(arom)); 7.29–7.25 (m, 2H, HC(arom)); 7.24–7.20 (m, 1H, HC(arom)); 4.83, 4.50 (AB, J_{AB} = 9.6, 2H, H_2C). ^{13}C NMR ($CDCl_3$): δ 157.3, 138.5, 134.5, 133.6, 130.2, 130.2, 129.1, 128.9, 128.3, 128.2, 127.3, 127.1, 126.9, 125.9, 121.8 (15 CH(arom), 3 C(arom), 3 C(imid)); 125.3 (q, $^1J_{C,F}$ = 280.9, CF_3); 92.0 (q, $^2J_{C,F}$ = 30.5, *C*CF_3); 51.2 (CH_2). ^{19}F NMR ($CDCl_3$): δ –80.7. HR-ESI-MS: 407.13492 (calcd 407.13657 for $C_{24}H_{18}ON_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +48 (c 1.0, CH_2Cl_2).

*(*R*)-2,5,6-Triphenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*R*)-**8a**). Yield: 0.327 g (83%). Colorless oil. IR (film): ν 3061br.m, 2926m, 1606s, 1589s, 1572s, 1500s, 1443s, 1340s, 1305s, 1197vs, 1174vs, 1063s, 1009s, 974s, 915m, 738s, 699s. ^{1}H NMR

($CDCl_3$): δ 7.64–7.61 (m, 2H, HC(arom)); 7.60–7.57 (m, 2H, HC(arom)); 7.53–7.50 (m, 3H, HC(arom)); 7.43–7.35 (m, 5H, HC(arom)); 7.29–7.25 (m, 2H, HC(arom)); 7.23–7.20 (m, 1H, HC(arom)); 4.83, 4.50 (AB, J_{AB} = 9.6, 2H, H_2C). ^{13}C NMR ($CDCl_3$): δ 157.3, 138.5, 134.5, 133.6, 130.2, 130.2, 129.1, 128.9, 128.3, 128.2, 127.3, 127.1, 126.9, 125.9, 121.8 (15 CH(arom), 3 C(arom), 3 C(imid)); 125.3 (q, $^1J_{C,F}$ = 282.5, CF_3); 92.0 (q, $^2J_{C,F}$ = 30.5, CCF_3); 51.2 (CH_2). ^{19}F NMR ($CDCl_3$): δ –80.7. HR-ESI-MS: 407.13519 (calcd 407.13657 for $C_{24}H_{18}ON_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –50 (c 1.0, CH_2Cl_2).

*2-(4-Methoxyphenyl)-5,6-diphenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*RS*)-**8b**). Yield: 0.349 g (80%). Colorless crystals. Mp. 202–204 °C. IR (KBr): ν 3432br.m, 2967w, 2844w, 1606s, 1588s, 1572s, 1518s, 1500s, 1443m, 1346m, 1310s, 1251s, 1175vs, 1063m, 1015m, 995s, 832m, 757m, 702s. ^1H NMR ($CDCl_3$): δ 7.61–7.58 (m, 2H, HC(arom)); 7.55–7.52 (m, 2H, HC(arom)); 7.43–7.35 (m, 5H, HC(arom)); 7.29–7.25 (m, 2H, HC(arom)); 7.24–7.19 (m, 1H, HC(arom)); 7.03–6.99 (m, 2H, HC(arom)); 4.79, 4.47 (AB, J_{AB} = 9.6, 2H, H_2C); 3.86 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 160.9, 157.3, 138.5, 134.5, 130.2, 129.1, 128.3, 128.2, 128.1, 127.4, 127.1, 126.9, 125.4, 121.8, 114.4 (14 CH(arom), 4 C(arom), 3 C(imid)); 123.4 (q, $^1J_{C,F}$ = 282.4, CF_3); 92.0 (q, $^2J_{C,F}$ = 31.4, CCF_3); 55.4 (CH_3); 51.2 (CH_2). ^{19}F NMR ($CDCl_3$): δ –81.0. HR-ESI-MS: 437.14628 (calcd 437.14714 for $C_{25}H_{20}O_2N_2F_3$, $[M+H]^+$).

*(*S*)-2-(4-Methoxyphenyl)-5,6-diphenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*S*)-**8b**). Yield: 0.371 g (85%). Colorless oil. IR (film): ν 3061br.m, 1606s, 1588s, 1572s, 1517s, 1501s, 1443s, 1307s, 1254s, 1178vs, 1020s, 1001s, 974m, 831s, 735s, 700s. ^1H NMR ($CDCl_3$): δ 7.60–7.57 (m, 2H, HC(arom)); 7.55–7.53 (m, 2H, HC(arom)); 7.43–7.35 (m, 5H, HC(arom)); 7.29–7.25 (m, 2H, HC(arom)); 7.23–7.20 (m, 1H, HC(arom)); 7.03–7.00 (m, 2H, HC(arom)); 4.79, 4.47 (AB, J_{AB} = 9.6, 2H, H_2C); 3.86 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 160.9, 157.3, 138.5, 134.5, 130.2, 129.1, 128.3, 128.2, 128.1, 127.4, 127.1, 126.9, 125.4, 121.8, 114.4 (14 CH(arom), 4 C(arom), 3 C(imid)); 125.3 (q, $^1J_{C,F}$ = 279.8, CF_3); 92.0 (q, $^2J_{C,F}$ = 31.1, CCF_3); 55.4 (CH_3); 51.2 (CH_2). ^{19}F NMR ($CDCl_3$): δ –81.0. HR-ESI-MS: 437.14621 (calcd 437.14714 for $C_{25}H_{20}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +36 (c 1.0, CH_2Cl_2).

*(*R*)-2-(4-Methoxyphenyl)-5,6-diphenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*R*)-**8b**). Yield: 0.375 g (86%). Colorless crystals. Mp. 120–122 °C. IR (KBr): ν 3424br.w, 3058w, 2842w, 1606s, 1592s, 1573s, 1517s, 1501s, 1443m, 1341m, 1305s, 1253s,

1172vs, 1019s, 1000s, 974m, 829m, 770m, 701s. ^{1}H NMR ($CDCl_3$): δ 7.61–7.58 (m, 2H, HC(arom)); 7.55–7.52 (m, 2H, HC(arom)); 7.43–7.35 (m, 5H, HC(arom)); 7.29–7.25 (m, 2H, HC(arom)); 7.23–7.20 (m, 1H, HC(arom)); 7.03–6.99 (m, 2H, HC(arom)); 4.79, 4.47 (AB, J_{AB} = 10.2, 2H, H_2C); 3.86 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 160.9, 157.3, 138.5, 134.5, 130.2, 129.1, 128.3, 128.2, 128.1, 127.4, 127.1, 126.9, 125.4, 121.8, 114.4 (14 CH(arom), 4 C(arom), 3 C(imid)); 123.4 (q, $^{1}J_{C,F}$ = 282.8, CF_3); 92.0 (q, $^{2}J_{C,F}$ = 31.5, CCF_3); 55.4 (CH_3); 51.2 (CH_2). ^{19}F NMR ($CDCl_3$): δ –81.0. HR-ESI-MS: 437.14613 (calcd 437.14714 for $C_{25}H_{20}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –39 (c 1.0, CH_2Cl_2).

*(*S*)-(4-Methoxyphenyl)-5,6-dimethyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*S*)-**8c**). Yield: 0.156 g (50%). Colorless oil. IR (film): ν 3294br.w, 2933w, 2838w, 1774w, 1730m, 1692m, 1613m, 1515m, 1302m, 1258m, 1176m, 1030m, 834m, 732m. ^{1}H NMR ($CDCl_3$): δ 7.41–7.37 (m, 2H, HC(arom)); 6.91–6.87 (m, 2H, HC(arom)); 4.53, 4.20 (AB, J_{AB} = 9.5, 2H, H_2C); 3.75 (s, 3H, H_3C); 1.98 (s, 6H, 2 H_3C). ^{13}C NMR ($CDCl_3$): δ 160.8, 155.7, 133.8, 127.4, 115.2, 114.4, 114.2 (4 CH(arom), 2 C(arom), 3 C(imid)); 125.0 (q, $^{1}J_{C,F}$ = 285.2, CF_3); 91.6 (q, $^{2}J_{C,F}$ = 31.3, CCF_3); 55.4 (CH_3); 50.2 (CH_2); 13.1 (CH_3); 8.7 (CH_3). ^{19}F NMR ($CDCl_3$): δ –80.9. HR-ESI-MS: 313.11573 (calcd 313.11584 for $C_{15}H_{16}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +18 (c 1.0, CH_2Cl_2).

*(*R*)-2-(4-Methoxyphenyl)-5,6-dimethyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*R*)-**8c**). Yield: 0.152 g (49%). Colorless oil. IR (film): ν 3269br.w, 2923w, 2841w, 1777w, 1717m, 1682m, 1616m, 1518m, 1306m, 1261m, 1173m, 1030m, 831m, 736w. ^{1}H NMR ($CDCl_3$): δ 7.40–7.37 (m, 2H, HC(arom)); 6.90–6.87 (m, 2H, HC(arom)); 4.53, 4.20 (AB, J_{AB} = 9.5, 2H, H_2C); 3.75 (s, 3H, H_3C); 1.98 (s, 6H, 2 H_3C). ^{13}C NMR ($CDCl_3$): δ 160.8, 155.6, 133.8, 127.4, 115.2, 114.5, 114.1 (4 CH(arom), 2 C(arom), 3 C(imid)); 125.1 (q, $^{1}J_{C,F}$ = 285.2, CF_3); 91.6 (q, $^{2}J_{C,F}$ = 31.4, CCF_3); 55.4 (CH_3); 50.2 (CH_2); 13.1 (CH_3); 8.7 (CH_3). ^{19}F NMR ($CDCl_3$): δ –80.9. HR-ESI-MS: 313.11591 (calcd 313.11584 for $C_{15}H_{16}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –20 (c 1.0, CH_2Cl_2).

*(*S*)-2-(4-Methoxyphenyl)-6-methyl-5-phenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*S*)-**8d**). Yield: 0.295 g (79%). Colorless oil. IR (film): ν 3296br.w, 3063w, 2926w, 2856w, 1783m, 1713m, 1654m, 1593m, 1450m, 1308m, 1178m, 1011m, 739m, 702w. ^{1}H NMR ($CDCl_3$): δ 7.42–7.39 (m, 2H, HC(arom)); 7.36–7.32 (m, 2H, HC(arom));

7.23–7.19 (m, 3H, HC(arom)); 6.91–6.87 (m, 2H, HC(arom)); 4.70, 4.37 (AB, J_{AB} = 9.8, 2H, H_2C); 3.75 (s, 3H, H_3C); 2.22 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 160.9, 157.1, 136.3, 130.2, 128.9, 127.4, 126.8, 126.7, 125.5, 121.6, 114.3 (9 CH(arom), 3 C(arom)), 3 (C(imid)); 123.4 (q, $^1J_{C,F}$ = 282.3, CF_3); 91.9 (q, $^2J_{C,F}$ = 31.3, CCF_3); 55.4 (CH_2); 51.6 (CH_3); 14.6 (CH_3). ^{19}F NMR ($CDCl_3$): δ –81.6. HR-ESI-MS: 375.13269 (calcd 375.13149 for $C_{20}H_{18}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +29 (c 1.0, CH_2Cl_2).

*(*R*)-2-(4-Methoxyphenyl)-6-methyl-5-phenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole* ((*R*)-**8d**). Yield: 0.299 g (80%). Colorless oil. IR (film): ν 3292br.w, 3063w, 2926w, 2856w, 1780w, 1716w, 1593w, 1450w, 1308w, 1177w, 1011w, 738w, 700w. ^1H NMR ($CDCl_3$): δ 7.42–7.39 (m, 2H, HC(arom)); 7.36–7.32 (m, 2H, HC(arom)); 7.23–7.18 (m, 3H, HC(arom)); 6.91–6.87 (m, 2H, HC(arom)); 4.70, 4.37 (AB, J_{AB} = 9.8, 2H, H_2C); 3.76 (s, 3H, H_3C); 2.22 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 160.9, 157.1, 136.2, 130.2, 128.9, 127.4, 126.9, 126.7, 125.5, 121.6, 114.3 (9 CH(arom), 3 C(arom)), 3 (C(imid)); 123.4 (q, $^1J_{C,F}$ = 282.4, CF_3); 91.9 (q, $^2J_{C,F}$ = 32.1, CCF_3); 55.4 (CH_2); 51.6 (OCH_3); 14.5 (CH_3). ^{19}F NMR ($CDCl_3$): δ –81.6. HR-ESI-MS: 375.13295 (calcd 375.13149 for $C_{20}H_{18}O_2N_2F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –30 (c 1.0, CH_2Cl_2).

*(*S*)-5-Methyl-2-phenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole-6-carboxylic acid phenylamide* ((*S*)-**8e**). Yield: 0.313 g (81%). Colorless crystals. Mp. 148–150 °C. IR (KBr): ν 3378w, 3361w, 1697s, 1614s, 1594s, 1523s, 1491s, 1441s, 1380m, 1302m, 1210s, 1173s, 1065m, 1007m, 904w, 761m, 698m. ^1H NMR ($CDCl_3$): δ 8.65 (s, 1H, NH); 7.58–7.55 (m, 2H, HC(arom)); 7.49–7.46 (m, 2H, HC(arom)); 7.43–7.40 (m, 3H, HC(arom)); 7.26–7.22 (m, 2H, HC(arom)); 7.02–6.97 (m, 1H, HC(arom)); 4.69, 4.37 (AB, J_{AB} = 10.2, 2H, H_2C); 2.48 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 154.1 (C=O); 161.3, 138.2, 133.0, 131.1, 130.5, 129.1, 128.9, 127.3, 125.8, 123.7, 119.5 (10 CH(arom), 2 C(arom), 3 C(imid)); 123.2 (q, $^1J_{C,F}$ = 282.2, CF_3); 92.4 (q, $^2J_{C,F}$ = 31.4, CCF_3); 49.7 (CH_2); 10.2 (CH_3). ^{19}F NMR ($CDCl_3$): δ –80.9. HR-ESI-MS: 388.12610 (calcd 388.12674 for $C_{20}H_{17}O_2N_3F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = +42 (c 0.1, CH_2Cl_2).

*(*R*)-5-Methyl-2-phenyl-2-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]oxazole-6-carboxylic acid phenylamide* ((*R*)-**8e**). Yield: 0.321 g (83%). Colorless crystals. Mp. 140–142 °C. IR (KBr): ν 3378m, 3361m, 1697s, 1613s, 1594s, 1523s, 1492s, 1441s, 1380m, 1303s, 1210s,

1174s, 1065m, 1007m, 904w, 792m, 761s, 698s. ^{1}H NMR ($CDCl_3$): δ 8.76 (s, 1H, NH); 7.67–7.65 (m, 2H, HC(arom)); 7.60–7.57 (m, 2H, HC(arom)); 7.53–7.51 (m, 3H, HC(arom)); 7.36–7.32 (m, 2H, HC(arom)); 7.12–7.08 (m, 1H, HC(arom)); 4.79, 4.47 (AB, J_{AB} = 10.2, 2H, H_2C); 2.59 (s, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 154.1 (C=O); 161.3, 138.2, 133.0, 131.1, 130.5, 129.1, 128.9, 127.3, 125.8, 123.7, 119.5 (10 CH(arom), 2 C(arom), 3 C(imid)); 123.2 (q, $^{1}J_{C,F}$ = 283.1, CF_3); 92.4 (q, $^{2}J_{C,F}$ = 31.6, CCF_3); 49.7 (CH_2); 10.2 (CH_3). ^{19}F NMR ($CDCl_3$): δ –80.9. HR-ESI-MS: 388.12610 (calcd 388.12674 for $C_{20}H_{17}O_2N_3F_3$, $[M+H]^+$). $[\alpha]_D^{25}$ = –41 (c 1.0, CH_2Cl_2).

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